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Targeted therapy in gynecologic cancers: Ready for prime time?

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1. Introduction: Unmet need

Each year, around 225 000 women are diagnosed with ovarian cancer and over 140 000 die [1]. Despite the recent advances in understanding the role of proper staging in early cases, maximal debulking efforts, and new modes and route of adjuvant (including intraperitoneal and dose-dense regimen), neoadjuvant, and palliative chemotherapeutic interventions, recurrences are inevitable and survival rates are still dismal in the advanced stages.

Similarly, cervical cancer remains a major killer of women in low-resource countries and in women of low socioeconomic status in high-resource countries. In 2012, 528 000 women were affected and 226 000 died of their disease [1]. Despite the recent advances in primary prevention (HPV vaccination) and secondary prevention (screening by cytology and/or HPV testing and subtyping), most women in low-resource countries have no access to either vaccination or screening, and still present at a late stage.

Although early-stage and locally advanced cancers may be cured with radical surgery, chemoradiotherapy, or both, these modalities are scare in low-resource countries. Moreover, patients with metastatic cancers and those with persistent or recurrent disease after platinum-based chemoradiotherapy have limited options [2,3]. In both of these cancers, new forms of therapy are needed.

Increasing knowledge of the genetic basis for various cancers has led to the development of new drugs that are tailored to these specific cancer pathways, while sparing normal cells and reducing the toxic adverse effects of classical chemotherapy.

2. Ovarian cancer

New treatment options for women with advanced ovarian cancer include antiangiogenic drugs and poly (ADP-ribose) polymerase (PARP) inhibitors. Others include vaccines and anti-PD-1/PD-L1 therapies.

2.1. Antiangiogenic therapies

Angiogenesis is the formation of new blood vessels from pre-existing ones. A balance between pro- and antiangiogenic signaling pathways is maintained so that angiogenesis is only switched on when required for healing.

This pathway is governed by the vascular endothelial growth factor receptors (VEGFRs). Three VEGFRs (VEGFR 1, 2, and 3) mediate the effects of their ligands; these ligands comprise a family of growth factors, VEGF A through E, that induce proliferation and migration of endothelial cells—the primary cell type involved in the formation of new blood vessels.

In principle, once a tumor exceeds 1 mm in diameter it cannot receive adequate nutrients or oxygen from surrounding tissues by diffusion alone and it must then stimulate new blood vessel formation to support further growth [4]. Tumor cells induce an angiogenic switch in response to hypoxia and genetic alterations and produce angiogenic growth factors that promote proangiogenic signaling pathways, such as the VEGF pathway. The new blood vessels help the tumor grow and provide potential routes for spread. VEGF signaling can be blocked at several levels.

Targeted therapies differ from chemotherapy because they do not induce direct cell kill but prolong time to progression. Objective responses are therefore, in general, low, but progression-free survival and overall survival can be prolonged anyway. In addition, since targeted therapies affect disease-specific alterations and not normal tissues, they can be used as maintenance therapy.

In 2004, the US Food and Drug Administration (FDA) approved bevacizumab, a monoclonal antibody targeting VEGF-A, for the first-line treatment of metastatic colorectal cancer in combination with standard chemotherapy. More recently, the US Gynecologic Oncology Group (GOG) 218 trial [5] and the European International Collaborative Ovarian Neoplasm (ICON) 7 trial [6] investigated the addition of bevacizumab to conventional chemotherapy in high-risk metastatic ovarian cancer with maintenance bevacizumab following chemotherapy. The two trials showed a significant benefit on progression-free survival and bevacizumab was approved by the European Medicines Agency (EMA). The EMA also approved the use of bevacizumab in platinum-sensitive recurrent ovarian cancer based on the OCEANS trial [7], which showed doubling of the progression-free survival. In addition, the FDA and the EMA also approved the use of bevacizumab in patients with recurrent, platinum-resistant ovarian cancer based on the phase III AURELIA trial [8], which demonstrated that bevacizumab with chemotherapy reduced the risk of disease progression by 52% compared with chemotherapy alone.

Currently, optimizing the use of bevacizumab is being investigated in several trials, including the optimal duration (AGO-OVAR-17/BOOST), and the optimal combination with dose-dense chemotherapy (GOG 262, OCTAVIA), with intraperitoneal chemotherapy (GOG 252), or with prior neoadjuvant chemotherapy (GOG 262, ROSiA). Because

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both the VEGF-dependent and Ang1/Ang2-Tie2-dependent angiogenesis pathways are active in ovarian cancer, other investigators are assessing predictive tumor markers using either clinical characteristics from the major trials or certain biological tumor markers, such as gene immune signatures [9], histological subtypes such as the proliferative and mesenchymal subgroups [10], and Ang 1 and Tie2 concentrations. Other active angiogenic agents are also under investigation; for example, trebananib, which blocks Ang 1 and 2 by preventing their binding to the Tie2 receptor differs from VEGF-targeted agents in terms of adverse effects, such as bowel perforation and hypertension. Its use was associated with improvements in progression-free survival in patients with recurrent epithelial ovarian cancer. However, other research involves targeting the VEGF-receptor signaling rather than its ligand.

Antiangiogenic therapy faces a number of barriers that limit its potential. The clinical benefit of these agents has been modest and they are associated with high costs, which significantly limit their use in most low-resource countries, and significant adverse effects such as hypertension, thrombotic events, and bowel perforation. Moreover, the role of angiogenesis in tumor development is clearly vastly more complex than originally believed and the interaction between the tumor, the vasculature, and the tumor microenvironment remains poorly understood.

Other agents that have been investigated with variable responses are pazopanib and cediranib. A phase II open-label study of pazopanib (given 800 mg daily, orally) was conducted in 36 women with recurrent ovarian cancer and an elevated CA125, who had previously had a complete CA125 response to platinum-based chemotherapy [11]. The authors reported that 11 (31%) women had a CA125 response, and progression-free survival at 6 months was 17% (95% CI, 6%−33%). A phase II study of daily cediranib in 47 women with recurrent ovarian cancer found the median progression-free survival was 5.2 months [12].

2.2. PARP inhibitors

PARP inhibitors rely on the sensitivity of cells containing a defect in homologous recombination pathways to PARP inhibition (e.g. those with BRCA mutations), which results in the death of target tumor cells while sparing normal cells. Three ongoing studies are currently investigating this sensitivity: ARIEL, SOLO, and NOVA. Recently, both the FDA and EMA approved olaparib, a PARP inhibitor, as a maintenance therapy to prevent recurrence in platinum-sensitive ovarian cancer on the basis of the phase III trial SOLO [13]. The manufacturer also submitted additional data supporting the use of olaparib in patients with BRCA-mutated ovarian cancer who have already received three or more chemotherapy treatments. Two other phase 3 trials are underway: the SOLO2 trial is evaluating olaparib versus placebo as a maintenance therapy; and the SOLO3 trial is evaluating olaparib compared with standard chemotherapy for relapsed disease.

2.3. Other biologically active agents

Immunotherapy using anti-PD-1–therapies (nivolumab) in relapsed platinum-resistant ovarian cancer resulted in a dose-dependent response rate of 20%−33% [14]. This can be used either with or without an anti-CTLA-4 antibody (ipilimumab). Other research involves using mTOR inhibitors, for clear cell cancers of the ovary and MEK inhibitors for low-grade serous cancers [15,16].

3. Cervical cancer

Tumor neovascularization, as reflected by an increased microvessel density and strong immunostaining for the endothelial-cell marker (CD31), is associated with an aggressive course in cervical cancer [2–4]. Moreover, patients with high-grade cervical dysplasia and invasive carcinoma have increased expression of VEGF and hypoxia-inducible factor 1α (HIF-1α) [17]. Invasion is noted when VEGF is up-regulated. On the one hand, oncogenic HPV subtypes enhance HIF-1α protein production and VEGF expression, while on the other, VEGF expression is diminished by silencing HPV E6 mRNA but not when p53 is silenced, which means that E6 induces VEGF through a p53-independent mechanism [18]. In addition, HIF-1α activity enhanced by E7 maps to its C-terminal and correlates with displacement by E7 of the histone deacetylases HDAC1, HDAC4, and HDAC7 [19].

Recently, the FDA and EMA approved bevacizumab in combination with paclitaxel plus either cisplatin or topotecan as a treatment for patients with persistent, recurrent, or metastatic cervical cancer, based on the extension of overall survival in the GOG 240 study [20]. Bevacizumab combined with chemotherapy increased overall survival by 3.7 months, from 12.9 to 16.8 months, compared with chemotherapy alone. Although this may be considered a small gain, it is hoped that with the development of newer agents, quality overall survival may be improved. Other VEGF and non-VEGF mediated compounds are currently under investigation; for example, pazopanib (a tyrosine kinase inhibitor that targets the VEGF receptor) and sorafenib (a multikinase inhibitor) are two such agents [21]. However, data are lacking on vascular disrupting agents (e.g. vadimezan) and agents that inhibit angiogenesis through non-VEGF-dependent pathways (e.g. the Tie2–angiopoietin-2 pathway). In addition, agents targeting non-angiogenic signal-transduction pathways including Wee1 checkpoint inhibitors and Notch γ-secretase inhibitors may be promising.

4. Other gynecologic cancers

The role of biologically active agents is less studied in other gynecologic cancers. Unlike ovarian or cervical cancers, almost 90% of women with endometrial cancer are treated by primary surgery with five-year survival rates of over 70% [22]. Even when endometrial cancer recurs, it can be salvaged by a combination of surgery and radiotherapy. However, despite advances in radiotherapy, surgery, and chemotherapeutic strategies, the prognosis of women with recurrent or advanced endometrial cancer is poor, with a median overall survival of approximately 7–10 months [23–25].

There is a pressing need to improve current treatment strategies. In endometrial cancer, the expression levels of VEGF correlate well with prognosis [26]. In a phase II trial of single-agent bevacizumab in recurrent endometrial cancer, 40.4% of patients had a progression-free survival of at least 6 months [27]. Numerous other targeted agents have been investigated with variable disappointing results in recurrent and metastatic endometrial cancer. These included aflibercept (VEGF Trap-Eye) with a high-affinity binding to VEGF-A, VEGF-B, and placental growth factor [28,29]; thalidomide with antiangiogenesis effect [30]; gefitinib and erlotinib, two tyrosine kinase inhibitors [31,32]; cetuximab, a monoclonal antibody against epidermal growth factor receptor (EGFR) [33]; trastuzumab and lapatinib, both EGFR type 2 (HER2)-related inhibitors that affect signal transduction [34–36]; and temsirolimus and ridaforolimus, which block the phosphoinositide 3-kinase/AKT/mTOR pathway [37,38]. Other kinase inhibitors studied are sunitinib, brivanib, sorafenib, and imatinib [39]. Other drugs target epigenetic regulation of various cancer genes [40,41]. Epigenetic regulations may be particularly important in type I endometrial cancer.

The generally lower response rates of various targeted agents as compared with standard chemotherapy (43.3%−87%) [41–44] may be due to the multiplicity of carcinogenetic pathways and associated genes. Thus suppression of a single molecule may not be enough. Resistance may be circumvented using combinations of molecular-targeted drugs, and through the use of combination with current chemotherapeutic agents and/or hormonal therapy.

5. Conclusion

The role of targeted therapy in gynecological cancers, like in many other cancers, remains elusive. The last decade has seen significant

progress in defining the role of various genetic pathways and the use of relevant agents. Few successes include the use of antiangiogenesis agents and PARP inhibitors in ovarian cancer. The use of various clinical and biochemical markers will help limit their use to those who will benefit the most.

Conflict of interest

M. Seoud received travel grants and honoraria from Roche for presenting at conferences. E. Lundqvist received honoraria from Roche, Boehringer-Ingelheim, and Merck Sharp & Dohme for presentations and from Astra Zeneca for participation on an advisory board.

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